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SHORT COMMUNICATION

Association between empty nose syndrome and laryngopharyngeal reflux disease: a preliminary cohort study

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Abstract

Objective To investigate the association between laryngopharyngeal reflux disease (LPRD) and Empty Nose Syndrome (ENS).

Methods Nasal and laryngopharyngeal reflux symptoms were investigated in patients with ENS. Symptoms were evaluated with reflux symptom score-12 (RSS-12), nasal obstruction symptom evaluation (NOSE), empty nose syndrome 6-item questionnaire (ENS6Q), empty nose syndrome index (ENSI), and sinonasal outcome tool-22 (SNOT-22). The anxiety and depression were assessed with the general anxiety disorder-7 (GAD-7), and patient health questionnaire-9 (PHQ-9). A study of association was conducted between demographics and patient-reported outcome questionnaires.

Results Forty-one ENS patients were included (20 females (48.8%)). The control groups included 27 patients with rhinitis/rhinosinusitis and 36 asymptomatic individuals. The ENSI and ENS6Q detected ENS in 97.6% and 90.2% of cases, respectively. The mean scores of ENSI, ENS6Q, RSS-12, NOSE, and SNOT-22 were significantly higher in the ENS group compared to controls. The prevalence of suspected LPRD was 90.2% in the ENS group, which was significantly higher compared to controls. The prevalence of mild, moderate, moderately severe, and severe depression in ENS patients was 7.3% ($n=3$), 4.9% ($n=2$), 39.0% ($n=16$), and 46.3% ($n=19$), respectively. RSS-12 reported significant and high associations with the ENS6Q ($r_s=0.939$; $p=.001$) and ENSI ($r_s=0.699$; $p=.001$).

Conclusion LPRD symptoms and prevalence were significantly higher in ENS patients compared to controls. Future controlled studies are needed to investigate the prevalence of LPRD in ENS patients through objective approaches (impedance-pH monitoring, nasal digestive enzyme measurements).

Keywords Empty nose syndrome · Rhinology · Nose · Reflux · Laryngopharyngeal · Nasopharyngeal · Gastroesophageal · Otolaryngology · Otorhinolaryngology · Head neck · Surgery

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Introduction

Empty nose syndrome (ENS) is a disabling disorder associated with a paradoxical perception of nasal obstruction despite the widened nasal airway [1]. The incidence of ENS remains unknown despite an increasing number of publications in the past decades [2]. The origin of ENS is primarily iatrogenic with symptoms developing within the months following the nasal surgery [3]. Most ENS patients complained of paradoxical nasal obstruction, dyspnea, suffocation, burning nose, crusts, and dryness, impairing their quality of life (QoL) [3]. The pathophysiological mechanisms underlying the development of ENS remain unclear. Several abnormalities were reported in the nasal airflow dynamics, air humidification and warming, mucociliary clearance, and trigeminal-related sensory function but it remains unclear why some patients with anatomical turbinate defects developed ENS, while others do not experience symptoms with similar anatomy [3]. A recent hypothesis paper suggested that laryngopharyngeal reflux disease (LPRD) could play a key role in the development of symptoms with the deposit of digestive enzymes in the nasal mucosa leading to injuries of the nasal cells involved in air humidification, warming, or sensory function, and modifications of the nasal microbiome that cannot heal the injured mucosa [4].

This preliminary study aimed to investigate the association between laryngopharyngeal reflux disease (LPRD) and Empty Nose Syndrome (ENS) symptoms.

Methods

Patients and setting

Nasal and laryngopharyngeal symptom evaluations were proposed for French-native ENS patients, and healthy individuals (control group). The ENS patients were recruited from a database of a patient organization (*Victimes du SNV*) between March 2024 and August 2024. The ENS diagnosis was based on a history of nasal surgery, tomodensitometry findings, and cotton test for some patients [5]. The control groups consisted of subjects without nasal surgery, rhinitis or rhinosinusitis (asymptomatic individuals), and patients with confirmed allergic rhinitis or chronic rhinosinusitis (EPOS criteria). Reflux history was not an exclusion criterion for control groups. Individuals with chronic alcohol consumption (> 3 IU/day), tobacco overuse, or severe psychiatric illnesses limiting the participation, were excluded.

Demographics, and symptom evaluations

Demographics, including gender, age, and comorbidities, were collected. Subjects completed the French versions of the Empty Nose Syndrome 6-Item Questionnaire (Fr-ENS6Q) [6], Empty Nose Syndrome Index (Fr-ENSI, Appendix 1) [7], Sinonasal Outcome Tool-22 (Fr-SNOT-22) [8], and Nasal Obstruction Symptom Evaluation (Fr-NOSE) [9]. The reflux symptom score-12 (RSS-12, Appendix 2) [10] was used to investigate the reflux symptoms. RSS-12 documents the severity and frequency of the 12 most prevalent LPRD symptoms. A score > 11 suggests LPRD, exhibiting a sensitivity of 94.5% and a specificity of 86.2%.[10] The ENS diagnosis can be suspected for a Fr-ENS6Q cutoff ≥12 for French-speaking ENS patients [6]. This threshold was associated with a sensitivity of 97.0% and a specificity of 94.0%, respectively. The threshold of Fr-ENSI associated with the highest sensitivity (93.9%) and specificity (90.9%) was > 23/60.[7]

The anxiety and depression symptoms were assessed with the French versions of the General Anxiety Disorder-7 (GAD-7) [11], and the Patient Health Questionnaire-9 (PHQ-9) [12]. GAD-7 is a validated and standardized patient-reported outcome questionnaire evaluating the severity of anxiety of patients from 0 to 21. The minimal, mild, moderate, and severe anxiety scores were 0–4, 5–9, 10–14, and 15–21, respectively [11]. PHQ-9 is a patient-reported outcome questionnaire measuring the severity of depression with minimal, mild, moderate, moderately severe, and severe depression scores as 1–4, 5–9, 10–14, 15–19, and 20–27, respectively [12].

Statistical methods

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 30,0; IBM Corp, Armonk, NY, USA). Clinical scores were compared between groups with Kruskal-Wallis test. The association between items was evaluated with the Pearson correlation coefficient. The consistency was considered low, moderate, and strong for $k < 0.40$, 0.40–0.60, and $k > 0.60$, respectively. Chi-square was used to identify potential associations between comorbidities, ENS, and reflux patterns. A level of significance of $p < .05$ was used.

Results

Forty-one ENS patients were included, accounting for 20 (48.8%) females and 21 (51.2%) males (Table 1). The mean age of ENS patients was 41.6 ± 12.5 years. In most

Table 1 Demographics and clinical findings

Features	ENS $N=41$	Rhinitis $N=27$	Asymptomatic $N=36$	Differences (p-value)
Age (mean, SD)	41.6 ± 12.5	45.8 ± 13.1	46.8 ± 17.3	NS
Gender (N, %)				
Females	20 (48.8)	23 (85.2)	26 (72.2)	0.005
Males	21 (51.2)	4 (14.8)	10 (17.8)	
Comorbidities				
Irritable bowel syndrome	11 (26.8)	4 (14.8)	3 (8.3)	NS
Asthma	9 (22.0)	7 (25.9)	2 (5.6)	NS
Gastroesophageal reflux disease	9 (22.0)	5 (18.5)	7 (19.4)	NS
Autoimmune disorders	5 (12.2)	1 (3.7)	2 (5.6)	NS
Chronic obstructive pulmonary disease	3 (7.3)	1 (3.7)	0 (0)	NS
Heart disease	3 (7.3)	0 (0)	1 (2.8)	NS
Hypertension	3 (7.3)	5 (18.5)	4 (11.1)	NS
Arthrosis	3 (7.3)	2 (7.4)	6 (16.7)	NS
Osteoporosis	2 (4.9)	0 (0)	3 (8.3)	NS
Thyroid disorder	1 (2.4)	3 (11.1)	4 (11.1)	NS
Anemia	1 (2.4)	0 (0)	1 (2.8)	NS
Diabetes	0 (0)	1 (3.7)	3 (8.3)	NS
Liver disorder	0 (0)	1 (3.7)	0 (0)	NS
PROMs				
ENSI (mean, SD)	43.9 ± 12.6	16.9 ± 10.5	6.6 ± 7.1	0.001
ENS6Q (mean, SD)	21.4 ± 5.8	7.0 ± 5.4	3.5 ± 3.3	0.001
RSS-12 (mean, SD)	125.1 ± 71.3	47.0 ± 34.9	24.7 ± 32.0	0.001
NOSE (mean, SD)	13.8 ± 5.2	9.3 ± 5.5	2.8 ± 3.6	0.001
SNOT-22 (mean, SD)	72.3 ± 20.8	49.4 ± 20.3	25.2 ± 16.3	0.001

Table 1 footnotes: Kruskal Wallis test and Chi-square were used to compare groups. Abbreviations: ENS = empty nose syndrome; ENS6Q = empty nose syndrome 6-outcome questionnaire; ENSI = empty nose syndrome index; NOSE = nasal obstructive symptom evaluation; NS = non significant; PROM = patient reported outcome questionnaire; RSS-12 = reflux symptom score-12; SD = standard deviation; SNOT-22 = sinonasal outcome tool-22.

Table 2 Empty nose syndrome etiology and diagnosis

Outcomes	*N* (%)
Diagnosis (N, %)	
Nasofibroscopy	7 (17.1)
Nasofibroscopy & CT scan	13 (31.7)
Nasofibroscopy & Cotton test	7 (17.1)
Nasofibroscopy & Cotton test & CT scan	14 (34.1)
Etiologies (N, %)	
Septoplasty & inferior turbinoplasty	17 (41.5)
Septoplasty, inferior turbinoplasty, & FESS	12 (29.3)
Turbinoplasty without septoplasty	8 (19.5)
Septorhinoplasty & inferior turbinoplasty	3 (7.3)
Frontal osteoma & middle turbinectomy	1 (2.4)

Table 2 footnotes: Abbreviations: CT = computed tomography; FESS = functional endoscopic sinus surgery; N = number.

cases, the diagnosis was based on a nasofibroscopy, cotton test, and the exclusion of another sinus disease at the sinus tomodensitometry (Table 2). The procedures associated with the development of ENS included septoturbinoplasty, septoturbinoplasty and functional endoscopic sinus surgery, and turbinoplasty without septoplasty (Table 2).

The control groups included 27 patients with allergic rhinitis (=20) or chronic rhinosinusitis ($n=7$) and 36 asymptomatic individuals. The demographics and clinical features of individuals are reported in Table 1. The proportion of females was significantly higher in the rhinitis group compared to the ENS group. The diagnosis findings of ENS patients are available in Table 2. The primary comorbidities associated with ENS included allergy, irritable bowel syndrome, asthma, and a history of gastroesophageal reflux disease (GERD; Table 1). The ENSI and ENS6Q detected ENS in 97.6% and 90.2% of cases, respectively. The prevalence of suspected LPRD was 90.2% in the ENS group, which was significantly higher compared to controls (69.8%). The mean scores of ENSI, ENS6Q, RSS-12, NOSE, and SNOT-22 were significantly higher in ENS group compared to controls (Table 1).

Table 3 describes the RSS-12 symptoms in patients and controls. All RSS-12 item scores were significantly higher in ENS group compared to controls. Note that asymptomatic and rhinitis/rhinosinusitis individuals reported comparable scores for dysphagia, halitosis, heartburn/regurgitations, abdominal pain, and breathing difficulties, while the rhinitis/rhinosinusitis group reported significantly higher scores for the others.

The prevalence of mild, moderate, moderately severe, and severe depression in ENS patients was 7.3% ($n=3$), 4.9% ($n=2$), 39.0% ($n=16$), and 46.3% ($n=19$), respectively. The PHQ9 data reported that 35 patients (85.4%) required psychological assessment. Anxiety was mild ($n=6$; 14.6%), moderate ($n=9$; 22.0%), and severe ($n=22$;

Table 3 Reflux symptom score features

	ENS	Rhinitis	Asymptomatic	Differences
RSS-12	*N*=41	*N*=27	*N*=36	(p-value)
1. Voice disorder	7.8±7.9	3.5±3.6	1.0±2.2	0.005
2. Throat pain or odynophagia	9.2±6.8	4.5±5.5	1.6±2.4	0.001
3. Dysphagia	8.1±7.9	1.9±3.4	0.9±2.4	0.001
4. Throat clearing	11.3±8.2	4.1±5.4	1.7±2.9	0.001
5. Globus sensation	10.9±8.5	3.3±5.4	0.9±2.1	0.001
6. Excess throat mucus	15.3±9.1	7.3±6.1	2.1±4.9	0.001
7. Halitosis	8.6±7.5	2.4±3.4	2.9±4.9	0.001
8. Heartburn, stomach acid coming up, regurgitations, burps, nausea	10.1±8.4	4.2±5.6	3.5±4.9	0.001
9. Abdominal pain or diarrheas	9.7±8.7	4.1±3.8	3.6±6.3	0.006
10. Indigesiton, abdominal distension and/or flatus	10.6±9.2	3.7±3.8	3.2±5.1	0.001
11. Cough after eating or lying down or daytime troublesome cough	9.3±8.9	4.0±5.3	1.8±3.4	0.004
12. Breathing difficulties, breathlessness, or wheezing	14.1±8.6	4.0±7.0	1.6±3.1	0.001
RSS-12 total score	125.1±71.3	47.0±34.9	24.7±32.0	0.001

Table 3 footnotes: Abbreviations: N=number; RSS-12=reflux symptom score-12.

Table 4 Association analysis

PROM	RSS-12	ENSI	ENS6Q
NOSE	0.345 (p=.027)	0.509 (p=.001)	0.481 (p=.001)
ENSI	0.699 (p=.001)	-	0.939 (p=.001)
ENS6Q	0.939 (p=.001)	0.939 (p=.001)	-
SNOT-22	0.714 (p=.001)	0.769 (p=.001)	0.668 (p=.001)
PHQ-9	0.479 (p=.002)	0.481 (p=.002)	0.424 (p=.006)
GAD-7	0.545 (p=.001)	0.486 (p=.001)	0.477 (p=.002)
RSS-12	-	0.699 (p=.001)	0.939 (p=.001)

Table 4 footnotes: Abbreviations: ENS6Q=empty nose syndrome 6-outcome questionnaire; ENSI=empty nose syndrome index; NOSE=nasal obstructive symptom evaluation; PROM=patient reported outcome questionnaire; RSS-12=reflux symptom score-12; SNOT-22=sinonasal outcome tool-22.

53.7%), respectively. Thirty-one patients (75.6%) required assessment according to the GAD7 threshold.

The associations are reported in Table 4. RSS-12 reported significant and high associations with the ENS6Q (r_s=0.939; p=.001) and ENSI (r_s=0.699; p=.001).

Discussion

The ENS patients reported airflow and mucosa abnormalities, which are commonly associated with the development of severe nasal symptoms, including dryness, crusts, or paradoxical nasal obstruction. However, in practice, many patients underwent aggressive nasal surgery for recalcitrant chronic rhinosinusitis or malignancies without developing postoperative ENS symptoms, which makes unclear the etiology of symptoms of ENS patients [3, 4].

The preliminary clinical findings of the present study can support a high prevalence of LPRD symptoms in ENS patients (97.6%) and a significant association between the severity of LPRD and ENS symptoms. LPRD is characterized by the backflow of gastroduodenal content into the upper aerodigestive tract mucosa through gaseous, upright, and daytime weakly acid droplets [13]. From a histopathological standpoint, pepsin has been shown to decrease the mucosa expression of carbonic anhydrases, mucin, and other proteins involved in the hydration and protection of the mucosa against aggressions [14–16]. Interestingly, recent studies have shown that more than 50% of LPRD patients experience nasal symptoms and findings, including burning, crust, and dryness, which are found in ENS patients as well [17]. The significant association between LPRD and ENS symptoms in ENS patients could be explained by the post-surgical reduction of the posterior nasal obstruction, leading to a more important nasal exposure to reflux gaseous events [4]. The reduction of the nasal mucosa surface could be linked with a reduction of the nasal mucosa involved in the defense mechanisms against reflux. In other words, the remaining nasal mucosa surface could be not effective enough in protecting the mucosa against enzyme toxicity and ensuring nasal homeostasis and physiology. This hypothesis could indirectly support the findings of this preliminary study but requires future studies using objective reflux evaluations to be confirmed.

The levels of anxiety, depression, and related autonomic nerve dysfunction are high in the LPRD patient population [18]. Studies supported an association between autonomic nerve dysfunction and the increase in the number and duration of transient lower and upper esophageal sphincter relaxations, increasing the reflux events and the deposit of enzymes into the upper aerodigestive tract mucosa. The autonomic nerve dysfunction is therefore associated with a

vagal nerve dysfunction [19]. In the present study, there were significant associations between the severities of anxiety, depression, ENS, and reflux scores, which could support a potential role of autonomic nerve dysfunction mechanisms. However, it remains difficult to know if ENS and LPRD patients are primarily more anxious and depressive than controls, or if their symptoms lead to higher anxiety and depression levels compared to asymptomatic individuals.

The identification of a potential clinical association between ENS and LPRD symptoms can lead to the consideration of reflux disease as a potential contributing factor in the development of ENS. Thus, future controlled studies are needed to compare the prevalence of LPRD at the 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring, nasal detection of gastroduodenal enzymes, and mucosa abnormalities (expression of proteins and genes involved in the homeostasis and defense mechanisms) between ENS patients, subjects with a history of aggressive nasal surgery, and healthy individuals.

The lack of objective testing for confirming the LPRD diagnosis and detecting nasal gastroduodenal enzymes are the primary limitation of this study. However, this study was a primary step in the investigation of a potential relationship between ENS and LPRD, and the results can indicate the need to conduct future studies using these objective and costly approaches. The consideration of two control groups is the primary strength of the study because LPRD symptoms are non-specific and can be found in other ear, nose, and throat conditions (e.g., chronic rhinosinusitis, rhinitis) [20–22]. In that way, rhinitis/rhinosinusitis patients reported higher RSS-12 compared to asymptomatic individuals. The elevated RSS-12 in rhinitis/rhinosinusitis patients can be attributed to some symptoms, such as postnasal drip, and sticky mucus, which overlap those of LPRD [20]. Moreover, it is important to keep in mind that LPRD has been identified as a contributing factor to chronic rhinosinusitis or idiopathic rhinitis, meaning that these patients could potentially have LPRD as well. Importantly, despite the non-specificity of LPRD and rhinitis/rhinosinusitis symptoms, the RSS-12 was significantly higher in ENS patients compared to controls, suggesting potential greater involvement of reflux compared to rhinitis/rhinosinusitis. The use of validated and standardized patient-reported outcome questionnaires is an additional strength of the study because they were validated in large populations including control groups.

Conclusions

The laryngopharyngeal reflux disease symptoms are more prevalent and severe in ENS patients compared to patients with rhinitis or rhinosinusitis and asymptomatic individuals. The results of this preliminary study support a potential link between reflux and ENS, which needs to be confirmed in future studies using objective approaches to document LPRD (e.g., nasal enzyme measurements and impedance-pH monitoring).

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